American Journal of Medical Genetics 63:4–6 (1996)

Invited Editorial Comment

Evolution of the Bone Dysplasia Family

William A. Horton
Research Department, Shriners Hospital for Crippled Children, Portland, Oregon

The idea of bone dysplasia "families" emerged in the mid 1980s [Spranger, 1988]. As put forth by its principal proponent, J. Spranger, the concept was simple: similar bone dysplasias are pathogenetically related. He suggested that the concept would have two uses. The first was theoretical; it would guide investigators searching for pathogenetic mechanisms. If a mechanism were discovered in one member of a family, a similar mechanism should be sought in other members of the bone dysplasia family. The second was practical; if a certain radiographic pattern were recognized in a patient, it should suggest family-specific radiographic and biochemical tests to be performed which might lead to a diagnosis. Even if such testing were uninformative, knowledge about the family might be useful for management and counseling.

One of the first publications regarding bone dysplasia families listed seven families: dysostosis multiplex, osteogenesis imperfecta, achondroplasia, spondyloepiphyseal dysplasia (SED) congenita, Larsen-otopalatodigital dysplasia (OPD), Stickler-Kniest dysplasia, and diastrophic dysplasia [Spranger, 1988]. At the time relatively little was known about the pathogenesis of the members of the last five of these families; the basis of the classification was radiographic.

By the early 1990s the family concept had a major impact on the nomenclature of the disorders. Indeed, the number of named chondrodysplasias had steadily grown through the 1970s and 1980s to an almost unmanageable number. At a meeting of the international working group on bone dysplasias held in Bad Honnef, Germany in 1991, this upward trend was reversed by grouping disorders of qualitatively similar radiographic findings [International Working Group on Constitutional Diseases of Bone, 1992]. This classification listed 24 major groups of bone dysplasias. Many previously used clinical and genetic criteria, such as age of onset and inheritance pattern, were no longer considered allowing greater flexibility in grouping together disorders exhibiting different degrees of severity. For example, the achondroplasia family included thanatophoric dysplasia, which is lethal, and hypochondroplasia, which may be difficult to distinguish from normal. Similarly, diastrophic dysplasia and atelosteogenesis types 1 and 2 were classified together.

How bone dysplasia families were defined has evolved with time. It was recognized that other pathologic changes such as abnormalities of growth plate histology and electron microscopy and of growth plate cartilage biochemistry could be utilized to better define and to extend families and even expand the number of families [Rimoin and Lachman, 1993]. Such observations also provided insight into pathogenetic abnormalities that might underlie certain of the families.

Most recently, the concept has had to accommodate molecular genetics into a definition of the families. This is because the explosion of knowledge in this field has made it possible to group many disorders into families on the basis of what gene is mutated. In several instances, members of a previously defined family have been shown to have mutations of the same gene. For example, thanatophoric dysplasia, achondroplasia, and hypochondroplasia are all due to heterozygous mutations of the fibroblast growth factor receptor (FGFR3) gene [Shiang et al., 1994; Rousseau et al., 1995a; Bellus et al., 1995a; Tavormina et al., 1995; Rousseau et al., 1995b; Bellus et al., 1995b]. Similarly, diastrophic dysplasia and atelosteogenesis type 2 are due to homozygosity for mutations of the diastrophic dysplasia sulfate transporter (DTDST) gene [Hästbacka et al., 1994, 1996]. Mutations of this gene have also been found in achondrogenesis type IB [Superti-Furga et al., 1996].

In some instances the molecular genetics information has made it possible to consolidate and/or rearrange previous groups or at least of certain members of such groups. For instance, several members of the SED congenita group, Kniest-Stickler dysplasia group and other spondylo epi-(meta)-physeal dysplasia SE (M) D group (late onset SED, Strudwick dysplasia) can now be combined into disorders due to heterozygous mutations of COL2A1, the gene encoding type II collagen [Spranger et al., 1994; Vikkula et al., 1994; Winterpacht et al., 1993; Tiller et al., 1995; Brown et al., 1995]. Likewise, pseudoachondroplasia as a member of the latter group can now be reclassified with members of the multiple epiphyseal dysplasia (MED) group as disorders that result from mutations of the gene for cartilage oligomeric matrix protein (COMP) [Hecht et al., 1995; Briggs et al., 1995].

Received for publication January 2, 1996.

Address reprint requests to Dr. William A. Horton, Research Department, Shriners Hospital for Crippled Children, Portland, OR 97201.

Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

TABLE I. Evolution of Bone Dysplasia Classifications: Seventeen Disorders Selected to Illustrate the Changes With Time*

1983	1992	1996
Usually lethal before or after birth	Achondroplasia group	FGFR3 mutation group
Achondrogenesis type I	Thanatophoric dysplasia	Thanatophoric dysplasia
Achondrogenesis type II	Achondroplasia	Achondroplasia
Hypochondrogenesis	Hypochondroplasia	Hypochondroplasia
Thanatophoric dysplasias		
Atelosteogenesis	Achondrogenesis group	COL2A1 mutation group
	Achondrogenesis type IB	Achondrogenesis type II
Usually not lethal		Hypochondrogenesis
Achondroplasia	Atelosteogenesis/diastrophic dysplasia group	SED congenita
Diastrophic dysplasia		Kniest dysplasia
SED congenita	Atelosteogenesis type 2	Stickler dysplasia
Strudwick dysplasia	Diastrophic dysplasia	Strudwick dysplasia
Kniest dysplasia		SED late onset
	Kniest-Stickler group	
Identifiable in later life	Kniest dysplasia	DTDST mutation family
Hypochondroplasia	Stickler dysplasia	Achondrogenesis type IB
MED		Atelosteogenesis type 2
Pseudoachondroplasia	SED congenita group	Diastrophic dysplasia
SED—late onset	Achondrogenesis type II	
Stickler dysplasia	Hypochondrogenesis	COMP mutation family
Jansen MCD	SED congenita	MED
Schmid MCD		Pseudoachondroplasia
	Other SE (M) D group	
	SED late onset	COL10A1 mutation family
	Strudwick dysplasia	Schmid MCD
	Pseudoachondroplasia	
		PTHrPR mutation family
	Epiphyseal dysplasia group	Jansen MCD
	MED	
	Metaphyseal dysplasia group	
	Jansen MCD	
	Schmid MCD	

* Year of classifications is given at top. Abbreviations are from text.

It should be noted that some disorders grouped together because of similar radiographic findings have turned out to be associated with mutations of quite different genes. The best example is in the metaphyseal chondrodyplasia (MCD) group. Mutations of a gene encoding a G-protein transmembrane spanning receptor for the parathyroid hormone-related protein receptor (PTHrPR) have been found in Jansen metaphyseal dysplasia [Schipani et al., 1995], while mutations of the gene for type X collagen (COL10A1) have been detected in Schmid metaphyseal chondrodysplasia [Warman et al., 1993; Wallis et al., 1994; McIntosh et al., 1995].

Thus, the concept that bone dysplasias that look similar to clinicians probably have a similar pathogenesis and can be grouped into families has evolved over the past two decades mainly in terms of how such families are defined. The impact of this change on the classification of a few chondrodysplasias is depicted in Table I. The 1983 and 1992 designations were taken from the International Nomenclature of Constitutional Diseases of Bone classifications published in 1983 and 1992. The classifications were modified slightly to allow one to trace entities through the different schemes.

It is interesting that in 1988, Spranger [1988] pointed out difficulties in utilizing the bone dysplasia families concept to its full extent. The questions then centered around how shared radiographic manifestations could shed light on common pathogenetic mechanisms. The questions have now changed in their sophistication, but they sound familiar. They still center around how bone dysplasias arise. It is likely that careful investigation of how subtly different mutations of a gene produce subtly different clinical manifestations, an implication from the original concept, should help to resolve these questions.

ACKNOWLEDGMENTS

The writing of this paper was supported in part by grants from the Shriners Hospitals for Crippled Children (15957) and the National Institutes of Health (HD20691).

REFERENCES

Bellus G, Hefferon T, Oritz de Luna R, Hecht J, Horton W, Machado M, Kaitila I, McIntosh I, Francomano C (1995a): Achondroplasia is defined by recurrent G380R mutations in FGFR3. Am J Hum Genet 56:368–373.

Bellus GA, McIntosh I, Smith EA, Aylsworth AS, Kaitila I, Horton WA, Greenhaw GA, Hecht JT, Francomano CA (1995b): A recurrent mutation in the tyrosine kinase domain of fibroblast growth factor receptor 3 causes hypochondroplasia. Nat Genet 10:357–359.

Briggs MD, Hofman SMG, King LM, Olsen AS, Mohrenweiser H, Leroy JG, Mortier GR, Rimoin DL, Lachman RS, Gaines ES, Cek-

leniak JA, Knowlton RG, Cohn DH (1995): Pseudoachondroplasia and multiple epiphyseal dysplasia due to mutations in the cartilage oligomeric matrix protein gene. Nat Genet 10:330–336.

Brown D, Vandenburgh K, Kimura A, Weingeist T, Shetfield V, Stone E (1995): Novel frameshift mutations in the procollagen 2 gene (COL2A1) associated with Stickler syndrome (hereditary arthoophthalmopathy). Hum Molec Genet 4:141–142.

Hästbacka J, Superti-Furga A, Wilcox WR, Rimoin DL, Cohn DH, Lander ES (1996): Atelosteogenesis type II is caused by mutations in the diastrophic dysplasia sulfate transporter gene (DTDST): Evidence for a phenotypic series involving three chondrodysplasias. Am J Hum Genet 58:255–262.

Hästbacka J, de la Chapelle A, Mahtani MM, Clines G, Reeve-Daly MP, Daly M, Hamilton BA, Kusumi K (1994): The diastrophic dysplasia gene encodes a novel sulfate transporter: Positional cloning by fine-structure linkage disequilibrium mapping. Cell 78: 1073–1087.

Hecht JT, Nelson L, Crowder E, Wang Y, Elder F, Harrison W, Francomano C, Prange C, Lennon G, Deere M, Lawler J (1995): Mutations in exon 17B of cartilage oligomeric matrix protein (COMP) cause pseudoachondroplasia. Nat Genet 10:325–329.

International Working Group on Constitutional Diseases of Bone/Spranger J (1992): International classification of osteochondrodysplasias. Eur J Pediatr 151:407–415.

McIntosh I, Abbott MH, Francomano CA (1995): Concentration of mutations causing Schmid metaphyseal chondrodysplasia in the C-terminal noncollagenous domain of type X collagen. Hum Mutat 5:121–125.

Rimoin DL, Lachman RS (1993): Genetic disorders of the osseous skeleton. In Beighton P (ed): "McKusick's Heritable Disorders of Connective Tissue." St. Louis: Mosby, pp 557–690.

Rousseau F, Bonaventure J, Legeal-Mallet L, Pelet A, Rozet J, Maroteaux P, Le Merrer M, Munnich A (1995a): Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. Nature 371:252–254.

Rousseau F, Saugier P, Le Merrer M, Munnich A, Delezoide A, Maroteaux P, Bonaventure J, Narcy F, Sanak M (1995b): Stop codon FGFR3 mutations in thanatophoric dysplasia type I. Nat Genet 10:11–12.

Schipani E, Kruse K, Jüppner H (1995): A constitutively active mutant PTH-PTHrP receptor in Jansen-type metaphyseal chondrodysplasia. Science 268:98–100.

Shiang R, Thompson LM, Zhu Y-Z, Church DM, Fielder TJ, Bocian M, Winokur ST, Wasmuth JJ (1994): Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. Cell 78:335–342.

Spranger J (1988): Bone dysplasia "families." Pathol Immunopathol Res 7:76–80.

Spranger J, Winterpacht A, Zabel B (1994): The type II collagenopathies: A spectrum of chondrodysplasias. Eur J Pediatr 153:56–65.

Superti-Furga A, Hästbacka J, Wilcox WR, Cohn DH, van der Harten HJ, Rossi A, Blau N, Rimoin DL, Steinmann B, Lander ES, Gitzelmann R (1996): Achondrogenesis type IB is caused by mutations in the diastrophic dysplasia sulfate transporter gene. Nat Genet 12: 100–102.

Tavormina P, Shiang R, Thompson L, Zhu Y, Wilkin D, Lachman R, Wilcox W, Rimoin D, Cohn D, Wasmuth J (1995): Thanatophoric dysplasia (types I and II) caused by distinct mutations in fibroblast growth factor receptor 3. Nat Genet 9:321–328.

Tiller GA, Polumbo PA, Weis MA, Bogaert R, Lachman RS, Cohn DH, Rimoin DL, Eyre DR (1995): Dominant mutations in the type II collagen gene, COL2A1, produce spondyloepimetaphyseal dysplasia, Strudwick type. Nat Genet 11:87–89.

Vikkula M, Metsaranta M, Ala-Kokko L (1994): Type II collagen mutations in rare and common cartilage diseases. Ann Med 26:107–114.

Wallis GA, Rash B, Sweetman WA, Thomas JT, Super M, Evans G, Grant ME, Boot-Handford RP (1994): Amino acid substitutions of conserved residues in the carboxylterminal domain of the alpha 1 (X) chain of type X collagen occur in two unrelated families with metaphyseal chondrodysplasia type Schmid. Am J Hum Genet 54: 169–178.

Warman ML, Abbott M, Apte SS, Hefferson T, McIntosh I, Cohn DH, Hecht JT, Olsen BB, Francomano CA (1993): A type X collagen mutation causes Schmid metaphyseal chondrodysplasia. Nat Genet 5: 79–82.

Winterpacht A, Hilbert M, Schwarze U, Mundlos S, Spranger J, Zabel BU (193): Kniest and Stickler dysplasia phenotypes caused by collagen type II gene (COL2A1) defect. Nat Genet 3:323–326.